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Original Article

Real life practice of sweat testing in Europe

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Abstract

Evidence based guidelines exist for sweat testing, which remains a key component of a diagnosis of cystic fibrosis (CF), especially following newborn bloodspot screening (NBS). There are emerging challenges with respect to maintaining a valid sweat test service, notably a smaller number of sweat tests ordered in regions with established NBS programmes where Pediatricians refer less children for sweat testing, younger patients and equipment becoming obsolete. The ECFS Diagnostic Network Working Group has undertaken a comprehensive survey to better define sweat test practice across Europe. The survey was completed by 136 European respondents representing a CF center or laboratory providing a sweat test service (65% from regions with NBS for CF). There was considerable variance in practice, often not consistent with guidelines. In particular collection of sweat from two sites was rarely reported in European centres in contrast to US guidelines. There was a range of different references quoted for cut-off for both a positive and intermediate test. Most responses suggest cost is becoming an increasing issue and is not sufficiently reimbursed. This work will inform best practice guidelines and resources to sustain and improve sweat testing in Europe.

1. Introduction

The diagnosis of cystic fibrosis (CF) is made with one of the following presentations: characteristic clinical features, a family history of CF or a positive antenatal or newborn bloodspot CF screening (NBS) result. Confirmatory diagnostic tests are required and these should always include a sweat test, even when two CF causing mutations are identified of the Cystic Fibrosis Transmembrane Conductance Regulator (*CFTR*) gene [1–2]. Recent international consensus guidelines reduced the upper cut-off value for a normal sweat chloride to 30 mmol/L for all ages [1].

The sweat test requires experienced staff who can follow standard operating procedures. There are clear national and international guidelines available for laboratories providing a sweat test service [3–6]. For most people with CF the diagnosis is straightforward and the sweat test demonstrates the characteristically raised salt levels in the sweat (chloride being the most repeatable and reliable diagnostic measure) [7]. For some patients the diagnosis is less clear and in these cases, the sweat test result is important in guiding designation and management [8–10]. Moreover, recently published guidelines have changed the borderline cut-off chloride values to 30 mmol/L

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for all ages [1]. The sweat test also has a key role in the exclusion of a diagnosis of CF, given the extensive number of recognised *CFTR* mutations and the possibility of detecting new *CFTR* mutations. As such, sweat testing is a critical element of the follow-up of a positive newborn screening result, irrespective of the screening algorithm employed [11].

Providing a sweat test service has become increasingly challenging, particularly in regions that undertake NBS for CF. In these regions referrals for sweat testing are decreasing and those referred after NBS are by definition younger than 3 months of age [12]. In addition, equipment that has been used by many laboratories for decades is now becoming obsolete and commercially available systems have cost and training implications.

Results from different national CF registries in Europe demonstrate the significant number of patients with CF, who have either missing sweat test documentation or misdiagnosis of CF as a result of inadequate performance and false interpretation of sweat test [13–14]. Surveys conducted at national level have shown that monitoring the performance of laboratories and CF centres together with quality improvement initiatives improves the performance of sweat testing [15–17].

The aim of this project was to record current sweat test practice among Europe, to inform the requirements and contents of a future best practice document.

2. Methods

The questionnaire for the survey was developed by a core group of experts, referring to international guidelines and tested by another panel of experts (from the European CF Society (ECFS) Diagnostic Network and Neonatal Screening Working Groups). The questionnaire comprised 66 items covering six areas; 1) CF centre/laboratory details, 2) information provided to patient/parent/carers, 3) the method of sweat stimulation, 4) the method of sweat collection, 5) sweat analysis and 6) processing of the result. The questionnaire was in English, web-based and open from 15th October to 15th December 2015 to ECFS members, Cystic Fibrosis Europe members, national CF scientific societies and national sweat test working groups. Information on the project was disseminated several times and a help desk was established to assist participants, in particular with language issues. For three questions, there was overlap of potential responses, but respondents did not comment on this design error and the results were considered valid, as the questions were enquiring about approximate numbers (Table S1).

CF centres and laboratories were asked to send a scanned anonymised copy of their sweat test report sheet and the information leaflet (if available) for patients/parent/carers. Although informative responses were obtained from all over the globe (n = 143), only results from Europe (and Israel) were included in the analysis (n = 136). For the four countries with the highest number of respondents, the results were compared as a proportion of responses from each country (France, Germany, Italy and the United Kingdom). (Table 1).

3. Results

The survey was completed by 136 European sites across 29 countries (Fig. 1). For 127, the response jointly represented a CF centre and sweat test laboratory, for 8 a CF centre only and one respondent a laboratory only. The full questionnaire with responses is available (online Supplement Table S1) and the main findings are reported in this paper.

3.1. Institution and staff involved in test

Respondents represented CF centres of variable size and laboratories. The sweat test service was provided in a region with NBS for CF in the majority of respondents (65%). Sweat stimulation and collection was undertaken by laboratory technicians (49%), nurses (45%) and physiotherapist, physician, biologist and other laboratory staff (6%), most in a permanent employment (90%). Most respondents (72%) had considerable experience (>100 tests/year), although 42% reported undertaking <25 sweat tests pa/annum on infants with a positive NBS result. Nineteen percent indicated the cost of a sweat test (including staff) was less 20 Euros, for 30% between €20 and 50, for 26%

Table 1
Comparison of selected data from most represented countries (sites/country n=: France, 19; Germany, 25; Italy, 15; United Kingdom, 22).

Proportion of centres that:	France (%)	Germany (%)	Italy (%)	United Kingdom (%)
Are certified	100	88	80	86
Perform >100 tests per year	58	96	93	36
Have dedicated staff performing >30% of the total tests/year	53	72	87	68
Sweat test newborn screened babies	95	48	80	73
Report costs (including staff) <20 Euros	26	4	13	5
Receive reimbursement <20 Euros	58	56	67	5
Undertake bilateral testing	37	0	40	9
Use Wescor sweat inducer to stimulate sweat production	37	60	80	73
Collect sweat using a macroduct coil	37	84	13	82
Have a quantity not sufficient rate <5% in all ages	68	56	47	41
Have a quantity not sufficient rate <5% for infants <1 month of age	37	32	40	41
Use internal quality control as recommended	84	64	67	86
Participate in an external quality assurance scheme	74	24	44	46
Use <30 mmol/L as lower cut-off for normal sweat chloride	47	84	20	9
Use >60 mmol/L as the cut-off for a positive sweat chloride result	74	64	87	96

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Austria	2
Belgium	8
Croatia	1
Czech Republic	2
Denmark	1
Estonia	1
France	19
Germany	25
Greece	2
Hungary	1
Iceland	1
Israel	1
Italy	15
Latvia	1
Malta	1
Moldova	1
Norway	1
Poland	1
Portugal	3
Russia	1
Serbia	2
Slovenia	5
Spain	4
Sweden	3
Switzerland	4
The Netherlands	5
Turkey	2
Ukraine	1
United Kingdom	22

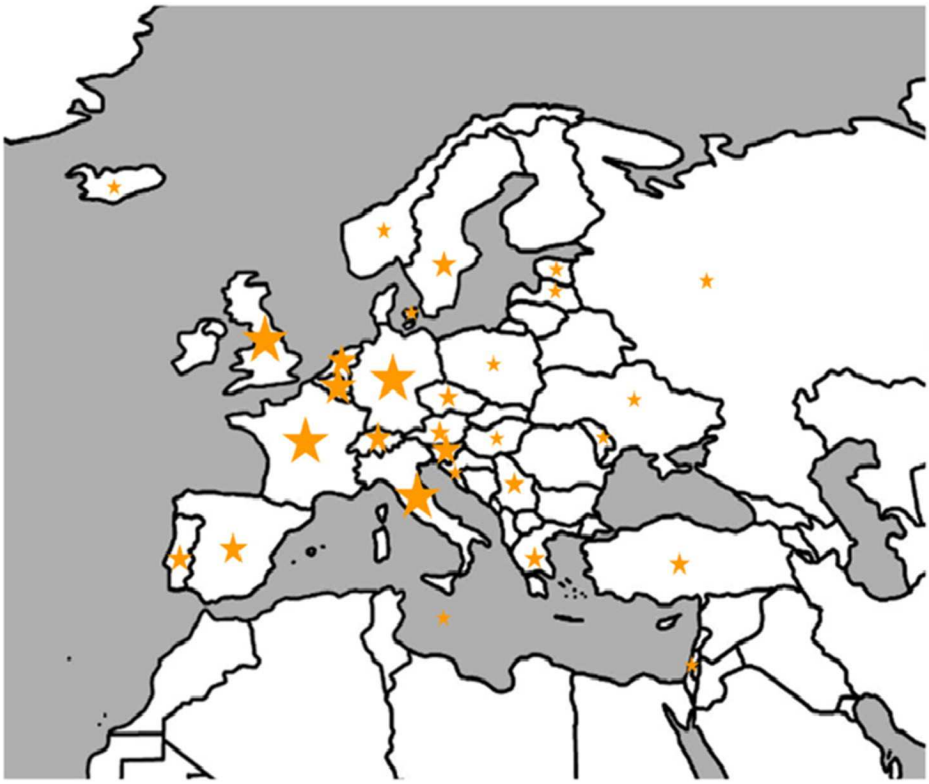

Fig. 1. Country distribution of participants in the ECFS diagnostic network working group sweat test survey 2015 (total n = 136).

between €50 and 100, for 11% between 100 and 300 Euros and for 14% total reimbursement was reported as unknown or absent. Sweat test reimbursement was reported as below €20 in 37% of participating sites (online Supplement Fig. S1). There was no reported difference in cost between regions with and without NBS programs.

3.2. Information for patient/parent/carers

Information about the sweat test performance was provided for patient/parent/carers in 95% cases (written information in 43%). The information was provided by the person collecting the sweat in 41%. In a small number (9%) informed consent was also taken.

3.3. Sweat stimulation by iontophoresis

The majority of respondents (51%) reported that sweat stimulation and collection was only undertaken from one site. Sweat stimulation was routinely undertaken on two different skin areas in 18% (7 sites from France, 5 from Italy, 4 from Belgium, 3 from UK, 1 from Denmark, 1 from Russia, 1 from Serbia, 1 from Spain, 1 from Switzerland,) and under special circumstances in 31% (for example, after a positive NBS result, if the distance travelled was far or if a previous sample was insufficient). The flexor surface of the forearm was the most common region chosen to stimulate sweat production (91%). Most services used a commercially available system to stimulate sweat production (70%). The lowest insufficient tests (QNS) rate in all ages was achieved with the Webster™ system (<5% QNS = 72%) and the lowest QNS rate for infants under 1 month of age with the Wescor™ sweat inducer (<10% QNS = 33%). Centres in regions with NBS program reported higher QNS rates compared to centres in regions without NBS program (<5% QNS in all ages: 56% vs 64%). Surfaces and equipment were correctly cleaned between each subject in 56% [18–19].

3.4. Sweat collection

Commercially available capillary tubes were used by 56% of respondents, only 48% for the recommended time of 30 min, 4% <20 min; 24% 20–30 min; 15% 30–45 min; 5% 45–60 min; 2% until Macroduct coil is full; 2% 35 min. For those respondents, 41% reported storing the pure sweat liquid collected in the capillary tube (either in the tubing or a sealed laboratory tube) and 50% reported that the sample was analyzed immediately. 95% of respondents reported a minimum age (range, 2–42 days) and/or a minimum weight (2–3.5 kg) below which they would not attempt sweat collection.

3.5. Sweat analysis

Analysis of samples was performed by laboratory staff in 85% (12% clinical staff; 3% other (biologist, physiotherapist, nurse) and 52% reported involvement with an external quality assurance scheme. For measurement of chloride from a liquid sample, the most reported method was coulometry using a chloridometer (54%). 68% of respondents reported only analyzing for sweat chloride, 16% for conductivity only and 16% for both.

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3.6. Inadequate sample collection and repeat testing

81% of respondents described performing at least a second sweat test to confirm a CF diagnosis (8% on the same day, range 1–28 days). For 43% the minimal acceptable volume for chloride analysis was reported as 20 μL: this is the minimum acceptable volume for the Macroduct™ conductivity method and for the analysis of chloride in undiluted sweat. 60% of the sites reported a failure rate (i.e. low sweat volume, quantity not sufficient) below 5% for all tested persons, although 38% for newborns (<1 month).

In the case of an insufficient sweat volume, sweat collection is repeated at another time in 77% of the cases (in 76% on another day).

3.7. Processing a sweat test result

Reference ranges quoted for interpretation of a sweat test result were variable. For the CF centres/laboratories that measure sweat chloride, only 18% reported using a different reference range for infants below 6 months of age. 60% sites used chloride negative range <30 mmol/L (29% of which used <40 mmol/L above 6 months of age); 53% sites used chloride intermediate range 30–59 mmol/L (22% of which used 40–59 mmol/L above 6 months of age); 68% sites used chloride positive range >60 mmol/L for all ages. In total, 12 different cut-offs for sweat chloride concentration were reported, ranging from <20 mmol/L to 50 mmol/L for a negative result and from 20 mmol/L to 90 mmol/L for an intermediate result. Variability for the reference ranges of other analytes (sodium, conductivity, osmolality) was more marked. A negative sweat test result is reported as "CF unlikely" by 74% of respondents, an intermediate result as "need for repeat sweat test" by 81% and a first positive result as "CF likely" which needs to be repeated" by 63%. All CF centres or laboratories used a written sweat test report. In most cases the diagnosis of CF was reported by a specialist doctor (87%).

Data from France, Germany, Italy and United Kingdom demonstrates some variation in approach of these countries (Table 1).

4. Discussion

This survey of real life practice across Europe provides evidence to support concerns around the increasing challenge of providing a high quality sweat service [9]. One of the main factors, the expansion of NBS for CF across Europe, has resulted in an overall change in referrals for sweat testing, alongside the challenge of collecting sweat from smaller infants [8]. For respondents providing a sweat test service in a screening area, the majority reported undertaking <50 sweat tests annually, which makes maintaining a high quality service difficult.

The country distribution of participants overall reflected the present situation of European sites providing CF care. We identified considerable variance in all aspects of the sweat test, from stimulation and collection, to analysis and how the result is communicated. Most notable was the variance with respect to obtaining sweat from two skin sites during a single test. Collecting from two sites is a clear recommendation from US guidelines but less so from European, where the circumstance of the sweat test is often stated as a factor [2–5]. A proportion of respondents stated that two collections would only be undertaken in special circumstances, for example if the family had travelled a long distance or the infant was particularly small. Some [20] but not all [21] retrospective data suggest that collection from two sites may reduce the "quantity not sufficient" test results, but given the time and resource implications of this strategy prospective studies are required to better determine the validity of this strategy.

Some of the variance identified reflects the development and evolution of sweat test techniques over the past 40 years. As equipment for the filter paper based collection techniques becomes obsolete, most units are moving to commercially available systems to collect sweat in a capillary tube. Such systems have facilitated more consistent standard operating procedures but this survey suggests that there continues to be variance in stimulation, collection times and processing (online Supplement Table S1). The move to commercially available kits has cost implications and this is illustrated by the survey, highlighting that reported costs are variable, but a significant factor for most.

Data from the four most represented countries demonstrate significant inconsistencies in approach despite national recommendations and regular audits (Table 1). Cost and insufficient reimbursement were repeatedly reported as factors influencing choice of equipment. These data can only partially explain differences within the most represented countries but can represent the basis for local audits.

The survey illustrates differences in processing and evaluation of results, with variance in the reference ranges employed and interpretation of guidelines. This highlights the need for more consistent global guidelines. Recent international initiatives on diagnostic recommendations will hopefully clarify this situation [1,22–23]. Measurement of conductivity is still regularly undertaken, despite being recommended only as a screening tool to exclude CF [3,24–26]. Most centres report subsequent analysis of sweat chloride in a laboratory to confirm a diagnosis. An important limitation of the survey design is represented by partially overlapping categories in 3/66 answers (sweat test cost and reimbursement, sweat collection time): having the same values for various categories, which is confusing even if the respondents are being asked for an estimate.

Although this survey illustrates considerable variance in practice and some areas of concern, it is apparent that excellent practice is somewhere achieved (existence of national recommendations, high rate of centres participating in an external quality assurance scheme, high rate of adherence to international sweat test recommendations and regular national sweat test auditing) and many resources have been developed across Europe to support the provision of a high quality service and clear communication with families. It is important that we utilise these resources and make them available in order that good practice is disseminated across Europe. We need to be able to address the challenges of maintaining high quality sweat test services by adopting a consistent and pragmatic approach.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcf.2017.09.002.

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